AD_____

Award Number: DAMD17-02-1-0226

TITLE: Phase I/II Study of Combination Neoadjuvant Hormone Therapy and Weekly OGX-011 (Clusterin Antisense Oligonulceotide) Prior to Radical Prostatectomy in Patients with Localized Prostate Cancer

PRINCIPAL INVESTIGATOR: Kim N. Chi, Ph.D.

CONTRACTING ORGANIZATION: University of British Columbia
Vancouver, British Columbia

REPORT DATE: Aug 2007

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
1-08-2007	Final	1 AUG 2002 - 31 JUL 2007

4. TITLE AND SUBTITLE

Phase II/III Study of Combination Neoadjuvant Hormone Therapy and Weekly OGX-011 (Clusterin Antisense Oligonulceotide) Prior to Radical Prostatectomy in Patients with Localized Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-02-1-0226

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Kim N. Chi, Ph.D.

E-Mail: kchi@bccancer.bc.ca

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of British Columbia
Vancouver, British Columbia

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
See attached page.

15. SUBJECT TERMS
Prostate Cancer, Clusterin, Antisense Oligonucleotide, Mthoxyethyl Gapmer

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	12	**19b. TELEPHONE NUMBER** *(include area code)*

The clusterin gene encodes a cytoprotective chaperone protein that promotes cell survival. Clusterin is expressed in a variety of cancers including prostate, increases in response to apoptotic stimuli, and confers a resistant phenotype. OGX-011 is a 2nd generation antisense complimentary to clusterin mRNA that inhibits expression of clusterin in xenograft models and thereby increases sensitivity to therapy. To evaluate OGX-011 as a potential treatment in humans, we have undertaken this Phase I/II study to evaluate the clinical, pathologic and biologic effects of OGX-011, in combination with neoadjuvant hormone therapy (NHT) in patients with prostate cancer and high risk features prior to radical prostatectomy. The primary objective of the phase I study was to determine phase II dose based on target regulation effect. The phase II component of this trial will assess the effects of combined NHT and OGX-011 on pathologic complete response. Progress: 25 patients were enrolled to 6 cohorts with doses of OGX-011 up to 640mg delivered. Toxicity was limited to grade 1/2, including fevers, rigors, fatigue and transient AST and ALT elevations and no dose-limiting toxicities. Plasma PK analysis showed dose proportional increases in AUC and Cmax with a t1/2 of approximately 2h. Prostate tissue concentrations of OGX-011 increased with dose, and tissue concentrations associated with preclinical effect could be achieved. Dose dependent decreases in prostate cancer cell clusterin expression were observed by QRT-PCR and immunohistochemistry (IHC). At 640mg dosing, clusterin mRNA was decreased to a mean of 8% (SD=4%) compared with lower dose levels and historical controls as assessed by QRT-PCR on laser captured microdissected cancer cells. By IHC, mean % cancer cells staining 0 intensity for clusterin protein at 640mg dosing was 54% (SD=24%). Dose-dependent changes in serum clusterin were also apparent. The recommended phase II dose for OGX-011 is 640mg based on target regulation results. The Phase II portion of this study, evaluating a 3-month neoadjuvant treatment with OGX-011 at the recommended phase II dose, enrolled the first patient June 2005. Twenty-four patients were accrued to the first stage: there have been no pathologic complete responses (primary endpoint) and the trial is now closed to accrual. Two episodes of unexpected toxicity with increased liver enzyme tests were encountered, however after protocol revisions no further treatment related serious adverse events were observed. Preliminary tissue pharmacokinetic data confirms a tissue half of the OGX-011 in the range of 7 days. Analyses of the correlative tissues (serum clusterin, serum pharmacokinetics, tissue clusterin expression, tissue pharmacokinetics) are being completed.

Table of Contents

INTRODUCTION

The *clusterin* gene on chromosome 8 encodes a chaperone protein which has been implicated in a variety of physiologic processes. Also known as *Testosterone repressed prostate message-2* [TRPM-2], or *sulfated glycoprotein-2*, *clusterin* is associated with numerous tumors including prostate [1], neuroblastoma [2], breast [3], lymphoma [4], urothelial [5] and renal cell carcinoma [6], and with various pathologic conditions including Alzheimer's [7] and nephrotoxic injury [8]. Clusterin levels increase dramatically during castration-induced apoptosis in rat prostate epithelial cells [9], in androgen dependent Shionogi tumors [10], and human prostate cancer CRW22 [11] and PC82 [12] xenografts. In human prostate cancer, clusterin levels are low or absent in most untreated hormone-naive tissues, but increase significantly within weeks after neoadjuvant hormone therapy [13]. Because clusterin binds to a wide variety of biological ligands [14,15], and is regulated by transcription factor HSF1 (heat shock factor 1) [16], the emerging view suggests that clusterin functions similarly to heat shock protein to chaperone and stabilize conformations of proteins at time of cell stress. Indeed, clusterin is substantially more potent than other HSP's at inhibiting stress-induced protein precipitation [17]. Significant differences exist, however, in amino acid sequence analysis which suggests that clusterin is a unique protein without any closely related family members yet identified. More recently, clusterin has been shown to inhibit the apoptosis inducing protein Bax, thus rendering cells more resistant to cell death [22].

Experimental and clinical studies in prostate cancer implicate clusterin with AI progression and with playing a protective role against apoptotic cell death from androgen withdrawal, chemotherapy and radiation [10,18.19,20]. OGX-011 is an ASO complementary to the *clusterin* mRNA. OGX-011 incorporates a phosphorothioate backbone with second-generation chemistry in the form of 2'-O-Methoxytheyl modifications to the 4 bases on either end of the 21-mer molecule. Such "gap-mer" modifications maintain the improved tissue pharmacokinetic profile of the second-generation chemistry but preserves high affinity for target mRNA and recruitment of RNase H necessary for activity. In pre-clinical models, OGX-011 improves the efficacy of chemotherapy, radiation, and androgen withdrawal by inhibiting expression of clusterin and enhancing the apoptotic response [10,19,20,21]. Furthermore, because of the second-generation chemistry and enhanced tissue half-life of OGX-011, more relaxed dosing schedules are possible while maintaining biologic efficacy of target inhibition. Rather than the prolonged continuous infusions of first generation phosphorothioate molecules that are usually employed, pre-clinical studies suggest that only weekly infusional dosing or less is required to maintain tissue levels of OGX-011 and target inhibition of clusterin [21], which is much more acceptable for patients in terms of tolerance and repeated administration.

To evaluate OGX-011 as a potential treatment in humans, we have undertaken this Phase I/II study to evaluate the clinical, pathologic and biologic effects of OGX-011, in combination with neoadjuvant hormone therapy in patients with prostate cancer and high risk features prior to radical prostatectomy. This primary objective of the phase I component of this trial is to define a recommended phase II dose of OGX-011 based on toxicity and maximal biologic effect. Secondary aims are to determine toxicity, the serum and tissue pharmacokinetic profile and measure evidence of OGX-011 effect on clusterin expression in tumor and peripheral blood mononuclear cells, and clusterin serum levels. The primary objective of the phase II component of this trial will assess the effects of combined neoadjuvant hormone therapy and OGX-011 for 3 months prior to radical prostatectomy on pathologic complete response.

A significant difficulty in the development of targeted therapy agents like OGX-011 is the determination of a biologically effective dose. The biologically effective dose can often be significantly different from that of the maximally tolerated dose, the usual endpoint in classically designed phase I trials. This study's phase I design allowed for a determination of an optimal biologically effective dose based on the target of interest (i.e. clusterin) within target tissue itself (i.e. prostate cancer) which has allowed for confidence in moving forward in phase II trials of the agent. The phase II portion of this study will serve to further define toxicity, confirm our observations of biological activity, and determine clinical activity of the recommended phase II dose of OGX-011 (i.e. 640 mg) in a larger group of patients.

BODY

TASK 1. STUDY INFRASTRUCTURE PREPARATION

- *Health Canada (Therapeutic Products Program) Investigational New Drug Submission*
- *Case Report Forms*
- *Medical and data monitoring*
- *Institutional Review Board*

All preparatory steps have been completed. Federal regulatory approval was given on 4 October 2002 (File Number 9427-N0711-98C). Initial University of British Columbia Research Ethics Board approval was granted October 24, 2002 (Number C02-0430), and HSRRB approval granted December 2002 (Number A-11279). Medical and Data monitoring and Case Report Form creation services were contracted with the National Cancer Institute of Canada - Clinical Trials Group.

TASK 2. PHASE I TRIAL

- *Patient enrollment*
- *Protocol treatment and dose escalation with OGX-011*
- *Define recommend phase II dose based on toxicity, serum and tissue pharmacokinetic and pharmacodynamic data*

TASK 4. SUPPORTING AND TRANSLATIONAL STUDIES

- *Serum pharmacokinetics*
- *Tissue pharmacokinetics*
- *Clusterin expression – prostate/tumor, mononuclear cells, serum*
- *Comparative molecular marker analysis in pathologic specimens*

As previously described in the 2005 Annual Report, these tasks have been completed for the phase I trial. To summarize, subjects (n = 25) with localized prostate cancer with high-risk features who were candidates for prostatectomy were treated with OGX-011 by 2-hour intravenous infusion on days 1, 3, and 5 and then weekly from days 8 – 29 combined with androgen blockade starting on day 1; prostatectomy was performed on days 30 – 36. Six different doses were tested, from 40 to 640 mg. OGX-011 plasma and prostate tissue concentrations were measured by an enzyme-linked immunosorbent assay method, and the pharmacokinetics of OGX-011 were determined from these data. Prostate cancer tissue, lymph nodes, and serial samples of peripheral blood mononuclear cells were assessed for clusterin expression using quantitative real-time polymerase chain reaction and immunohistochemistry. All statistical tests were two-sided. Only grade 1 and 2 toxicities were observed. The plasma half-life of OGX-011 was approximately 2 – 3 hours, and the area under the concentration versus time curve and *C* MAX (peak plasma concentration) increased proportionally with dose (P_{trend} <.001). OGX-011 in prostate tissue increased with dose (P_{trend} <.001). Dose-dependent decreases in prostate cancer and lymph node clusterin expression were observed by polymerase chain reaction of greater than 90% (P_{trend} = .008 and <.001, respectively) and by immunohistochemistry *(*P_{trend} <.001 and = .01, respectively). We concluded that OGX-011 was well tolerated and reduces clusterin expression in primary prostate tumors and that the optimal biologic dose for OGX-011 at the schedule used was 640 mg.

The manuscript was published in the Journal of the National Cancer Institute (J Natl Cancer Inst 2005;97:1287–96) which has one of the highest impact factors for cancer journals.

TASK 3. PHASE II TRIAL

- *Patient enrollment*
- *Phase II protocol treatment with OGX-011 (estimate 300g total drug)*
- *Efficacy determination*
- *Pathologic complete response rate*
- *Characterize clusterin expression*
- *PSA nadir and recurrence*

All preparatory steps have been completed for the phase II trial. University of British Columbia – British Columbia Cancer Agency Research Ethics Board (UBC-BCCA REB) approval was granted 3 November, 2004 (Number R04-0092). Federal regulatory approval was given on 17 December 2004 (File Number 9427-B0877-32C). HSRRB final approval notification was received until May 4, 2005 (Number A-11279.2) which was a longer approval process than initially anticipated. Medical and Data monitoring and Case Report Form creation services were contracted out to private groups.

The first subject was enrolled and received their first protocol treatment on 15 June 2005. Eleven subjects were initially enrolled at a rate of 4-5 per month. However, in this first set of subjects, there were 2 subjects who experienced serious adverse events in the form of increased liver enzyme test elevations (Grade 3-4) requiring holding of protocol therapy. The subjects were otherwise asymptomatic with no other toxicities. After withdrawal from protocol therapy, the subjects liver enzyme elevations had resolved and both patients went on to complete their prostatectomies without incident.

Due to these adverse events, the protocol was revised in the following manner:

1) Flutamide was replaced with bicalutamide, given its lower incidence of toxicity and the phase I experience of successfully changing from flutamide to bicalutamide in the face of Grade 1 or 2 elevated liver enzymes.
2) Patients that developed AST, ALT or bilirubin elevations were to have OGX-011 dose modifications and be prescribed a short course of dexamethasone.
3) Biochemistry lab testing was to be performed on a weekly basis in cycle 1, 2 and 3 (instead of every 2 weeks during cycle 2 and 3) to more closely monitor liver enzymes and other lab tests.

Approval was granted by Health Canada and the local REB by January 2006. Approval from the HSRRB was granted in June of 2006. In total, 24 patients were accrued to the first stage with the last patient completing protocol therapy in June, 2007. No further drug related serious adverse events have been observed.

The primary purpose of this phase II study is to define the pathologic complete response (CR) rate of neoadjuvant androgen withdrawal plus OGX-011 in patients with untreated, high-risk prostate cancer. The study employed a two-stage accrual design to distinguish a true underlying response rate of 20%, signifying efficacy, from a true underlying response rate of 5% or less, signifying that the intervention is not effective (null hypothesis), with an alpha error of 0.05 and beta error of 0.10. Initially, 21 evaluable patients were to be assessed. If only 0 or 1 pathologic complete response were seen in this sample then the study was to be terminated. If two or more pathologic complete responses are seen, a second cohort of 20 eligible patients would have been entered. Of the 24 patients enrolled, 21 completed the OGX-011 neoadjuvant treatment protocol. Of these 21, 20 underwent prostatectomy, and none was found to have had a complete pathologic response. One patient received radical radiotherapy, but clinically had disease prior to his radiotherapy. Thus, the criterion to open the second stage was not met and accrual stopped.

Preliminary tissue pharmacokinetic data on the first 11 patients enrolled to the study is shown in Figure 1 below. This demonstrates that concentrations of OGX-011 associated with biological activity are maintained up to 7 days post infusion.

As the last patient completed protocol therapy only in June 2007, to complete the correlative studies (prostatectomy tissues, serum and peripheral blood mononuclear cells) a final 1 year no-cost extension is being requested.

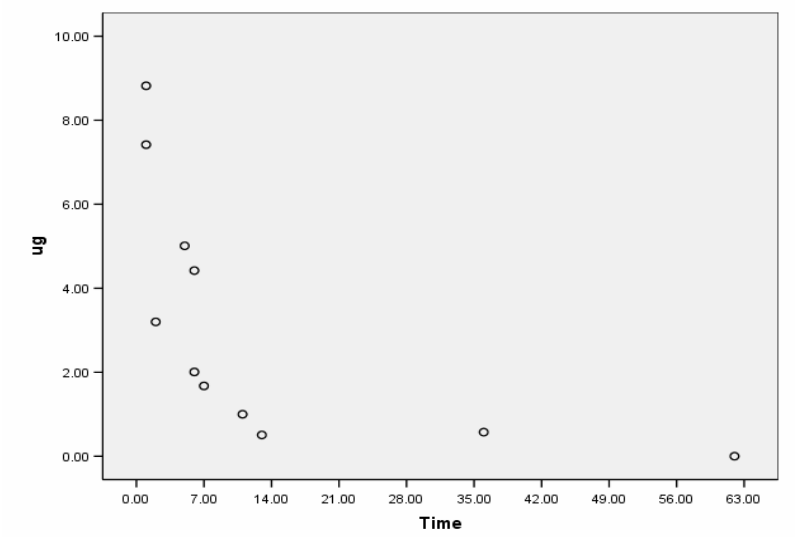

FIGURE 1. Prostate tissue concentration of OGX-011 vs. time from last OGX-011 dose. Circles represent individual patients.

KEY RESEARCH ACCOMPLISHMENTS:

- Completion of the first clinical trial of a second generation phosphorothioate antisense oligonucleotide in patients with cancer
- Novel study design using neoadjuvant therapy prior to radical prostatectomy. This design is now being used to evaluate pharmacodynamic effect of a number of other targeted agents.
- Proof of principal demonstration of biologic effect
- Determination of recommended phase II dose of OGX-011 based on biological efficacy. This dose is the basis for other trials involving OGX-011 in patients with lung, breast and hormone refractory prostate cancer.
- Phase II neoadjuvant trial has completed accrual and correlative studies are being completed.

REPORTABLE OUTCOMES:

Manuscripts

1. Chi KN, Eisenhauer E, Fazil L, Jones EC, Goldenberg SL, Powers J, Tu D, Gleave ME. A Phase 1 Pharmacokinetic and Pharmacodynamic Study of OGX-011, a 2'-Methoxyethyl Antisense Oligonucleotide to Clusterin in Patients with Localized Prostate Cancer. Journal of the National Cancer Institute, 97(17):1287-96, 2005.
2. Gleave M, Chi KN. Knock-down of the cytoprotective gene, clusterin, to enhance hormone and chemosensitivity in prostate and other cancers. Ann N Y Acad Sci. 2005; 1058:1-15.
3. Gleave M, Miyake H, Chi K. Beyond simple castration: targeting the molecular basis of treatment resistance in advanced prostate cancer. Cancer Chemother Pharmacol. 2005; 56 Suppl 1:47-57.
4. Sonpavde G, Chi KN, Powles T, Sweeney CJ, Hahn N, Hutson TE, Galsky MD, Berry WR, Kadmon D.Neoadjuvant therapy followed by prostatectomy for clinically localized prostate cancer. Cancer, In Press, 2007
5. Chi KN, Siu LL, Hirte H, Hotte SJ, Knox J, Kollmansberger C, Gleave M, Guns E, Powers J, Walsh W, Tu D, Eisenhauer E. A Phase I Study of OGX-011, a 2'Methoxyethyl Phosphorothioate Antisense to Clusterin, in Combination with Docetaxel in Patients with Advanced Cancer. Submitted to Clinical Cancer Research.

Abstracts

1. Chi KN, Eisenhauer E, Fazli L, Jones EC, Powers J, Hurtado-Coll A, Goldenberg SL, Gleave ME.A phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of OGX-011, a 2'methoxyethyl phosphorothioate antisense to *clusterin,* in patients with prostate cancer prior to radical prostatectomy. 16th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. Oral Presentation at the Proffered Papers Plenary Session, Geneva, September 2004. European Journal of Cancer Supplements. Volume 2, No. 8, September 2004.
2. J. J. Laskin, K. N. Chi, B. Melosky, K. Sill, D. Hao, C. M. Canil, M. Gleave, and N. Murray Phase I study of OGX-011, a second generation antisense oligonucleotide (ASO) to clusterin, combined with cisplatin and gemcitabine as first-line treatment for patients with stage IIB/IV non-small cell lung cancer (NSCLC) Journal Clinical Oncology (Meeting Abstracts) 2006 24: 17078.
3. K. N. Chi, S. J. Hotte, E. Yu, B. J. Eigl, I. Tannock, F. Saad, S. North, J. Powers, E. Eisenhauer, National Cancer Institute of Canada - Clinical Trials Group. A randomized phase II study of OGX-011 in combination with docetaxel and prednisone or docetaxel and prednisone alone in patients with metastatic hormone refractory prostate cancer (HRPC). Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 5069.

Presentations

1. "Clusterin Antisense". 4th International Congress on Targeted Therapies in Cancer. Washington, DC. August 26-28, 2005.
2. "Novel Agents: Endpoints and Trial Design". The Prostate Cancer Symposium (ASCO-ASTRO-SUO), February 22-24, 2007.

Book Chapters

1. Prostate Cancer: Translational and Emerging Therapies. Editors Nancy A. Dawson, W. Kevin Kelly, 2007. "What Antisene Oligonucleotides have Promise in Prostate Cancer" Kim N. Chi, Martin E. Gleave.

CONCLUSIONS

This phase I trial provides proof of principal evidence that OGX-011 can inhibit expression of clusterin in prostate cancer cells in humans. This is the first demonstration of dose dependent inhibition of a target, within target tissue by an antisense targeted therapeutic. Because of the successful determination of the biologically effective dose, phase II clinical trials with OGX-011 can move forward with confidence in the dosing regimen and schedule.

This trial has renewed interest in the antisense therapeutic platform, and several trials are moving forward with the second generation chemistry including antisense targeted against the cell survival proteins surviving and X-linked inhibitor of apoptosis using the data from the phase I trial of OGX-011 to support dosing.

Phase II trials using the recommended phase II dose of OGX-011 are now proceeding. In addition to the neoadjuvant phase II trial discussed above, four other trials using OGX-011 are currently enrolling patients: a randomized phase II trial of OGX-011 and docetaxel for patients with hormone refractory prostate cancer (grant funded by the National Cancer Institute of Canada), a randomized phase II trial of OGX-011 and mitoxantrone as second line therapy for patients with hormone refractory prostate cancer, a phase II trial of OGX-011 and docetaxel for patients with metastatic breast cancer, and a phase II trial of OGX-011 and Cisplatin-Gemciatbine for patients with advanced lung cancer.

REFERENCES:

1. STEINBERG J, OYASU R, LANG S, et al.: Intracellular levels of SGP-2 (Clusterin) correlate with tumor grade in prostate cancer. *Clinical Cancer Research*. (1997) **3**(10): 1707-11.
2. CERVELLERA M, RASCHELLA G, SANTILLI G, et al.: Direct transactivation of the anti-apoptotic gene apolipoprotein J (clusterin) by B-MYB. *Journal of Biological Chemistry*. (2000) **275**(28): 21055-60.
3. REDONDO M, VILLAR E, TORRES-MUNOZ J, TELLEZ T, MORELL M, PETITO CK: Overexpression of clusterin in human breast carcinoma. *American Journal of Pathology*. (2000) **157**(2): 393-9.
4. WELLMANN A, THIEBLEMONT C, PITTALUGA S, et al.: Detection of differentially expressed genes in lymphomas using cDNA arrays: identification of clusterin as a new diagnostic marker for anaplastic large-cell lymphomas. *Blood*. (2000) **96**(2): 398-404.
5. MIYAKE H, GLEAVE M, KAMIDONO S, HARA I: Overexpression of clusterin in transitional cell carcinoma of the bladder is related to disease progression and recurrence. *Urology*. (2002) **59**(1): 150-4.
6. PARCZYK K, PILARSKY C, RACHEL U, KOCH-BRANDT C: Gp80 (clusterin; TRPM-2) mRNA level is enhanced in human renal clear cell carcinomas. *Journal of Cancer Research & Clinical Oncology*. (1994) **120**(3): 186-8.
7. CALERO M, ROSTAGNO A, MATSUBARA E, ZLOKOVIC B, FRANGIONE B, GHISO J: Apolipoprotein J (clusterin) and Alzheimer's disease. *Microscopy Research & Technique*. (2000) **50**(4): 305-15.
8. ROSENBERG ME, SILKENSEN J: Clusterin and the kidney. *Experimental Nephrology*. (1995) **3**(1): 9-14.
9. MONTPETIT ML, LAWLESS KR, TENNISWOOD M: Androgen-repressed messages in the rat ventral prostate. *Prostate*. (1986) **8**(1): 25-36.
10. MIYAKE H, NELSON C, RENNIE PS, GLEAVE ME: Testosterone-repressed prostate message-2 is an antiapoptotic gene involved in progression to androgen independence in prostate cancer. *Cancer Research*. (2000) **60**(1): 170-6.
11. BUBENDORF L, KOLMER M, KONONEN J, et al.: Hormone therapy failure in human prostate cancer: analysis by complementary DNA and tissue microarrays. *Journal of the National Cancer Institute*. (1999) **91**(20): 1758-64.
12. KYPRIANOU N, ENGLISH HF, ISAACS JT: Programmed cell death during regression of PC-82 human prostate cancer following androgen ablation. *Cancer Research*. (1990) **50**(12): 3748-53.
13. JULY LV, AKBARI M, ZELLWEGER T, JONES EC, GOLDENBERG SL, GLEAVE ME: Clusterin expression is significantly enhanced in prostate cancer cells following androgen withdrawal therapy. *Prostate*. (2002) **50**(3): 179-88.
14. KOCH-BRANDT C, MORGANS C: Clusterin: a role in cell survival in the face of apoptosis? *Progress in Molecular & Subcellular Biology*. (1996) **16**: 130-49.
15. WILSON MR, EASTERBROOK-SMITH SB: Clusterin is a secreted mammalian chaperone. *Trends in Biochemical Sciences*. (2000) **25**(3): 95-8.
16. MICHEL D, CHATELAIN G, NORTH S, BRUN G: Stress-induced transcription of the clusterin/apoJ gene. *Biochemical Journal*. (1997) **328**(1): 45-50.
17. HUMPHREYS DT, CARVER JA, EASTERBROOK-SMITH SB, WILSON MR: Clusterin has chaperone-like activity similar to that of small heat shock proteins. *Journal of Biological Chemistry*. (1999) **274**(11): 6875-81.
18. SENSIBAR JA, SUTKOWSKI DM, RAFFO A, et al.: Prevention of cell death induced by tumor necrosis factor alpha in LNCaP cells by overexpression of sulfated glycoprotein-2 (clusterin). *Cancer Research*. (1995) **55**(11): 2431-7.
19. ZELLWEGER T, CHI K, MIYAKE H, et al.: Enhanced radiation sensitivity in prostate cancer by inhibition of the cell survival protein clusterin. *Clinical Cancer Research*. (2002) **8**(10): 3276-84.
20. MIYAKE H, CHI KN, GLEAVE ME: Antisense TRPM-2 oligodeoxynucleotides chemosensitize human androgen-independent PC-3 prostate cancer cells both in vitro and in vivo. *Clinical Cancer Research*. (2000) **6**(5): 1655-63.
21. ZELLWEGER T, MIYAKE H, COOPER S, et al.: Antitumor activity of antisense clusterin oligonucleotides is improved in vitro and in vivo by incorporation of 2'-O-(2-methoxy)ethyl chemistry. *Journal of Pharmacology & Experimental Therapeutics*. (2001) **298**(3): 934-40.
22. ZHANG H, KIM JK, EDWARDS CA, et al.: Clusterin inhibits apoptosis by interacting with activated Bax. *Nat Cell Biol.* (2005) **7**(9):909-15.